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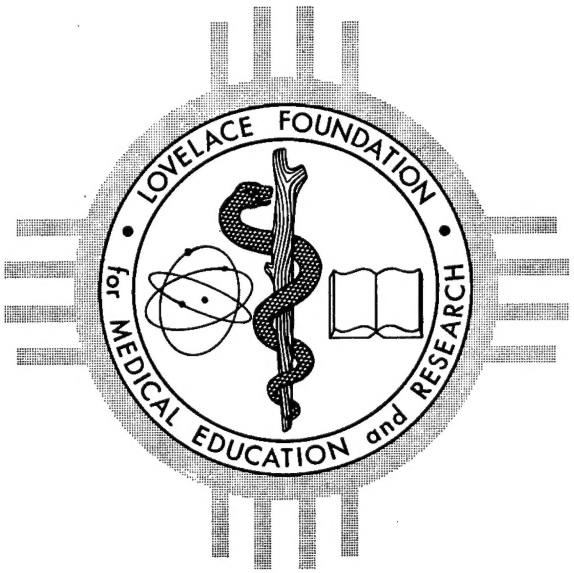

Albuquerque, New Mexico

LONG TERM WHOLE-BODY RETENTION AFTER HIGH LEVEL CESIUM-137 ADMINISTRATION TO RATS

by

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Robert G. Thomas and Randi Lie Thomas

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ABSTRACT

A long-term component of Cs-137 whole-body retention in rats has been found. The early retention kinetics, through approximately 120 days following intraperitoneal injection, show similarities to previously reported data from other investigators. However, use of higher levels of injected isotope has enabled measurement of body burdens for periods approaching one year and has resulted in discovery of a component of loss which has a half-life of 102 days. This retention component represents only 1.5×10^{-4} of the initial body burden and would not contribute significantly to the radiation dosage. It does, however, represent a fraction of whole-body retention which has not been reported for rodents and which may be present in other species. Certain broad physiological parameters such as age, body weight, and sex are discussed relative to the observed retention kinetics.

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Long Term Whole-Body Retention After High Level Cesium-137 Administration to Rats

Robert G. Thomas and Randi Lie Thomas

INTRODUCTION

Most studies on the retention kinetics of cesium in experimental animals have been time limited due to the short effective half-lives involved. Therefore, using tracer levels, long term quantitative determination of whole-body or organ radioactivity has been statistically infeasible with practical numbers of experimental animals and data collection is generally confined to a small post-administration segment of normal life span. Fortunately, due to species differences in cesium metabolism, larger mammals can be studied for longer times because of a general increase in effective half-time of elimination with increased body size (1, 2). For example, a factor of at least 20 difference was found in the long component of whole-body cesium retention between mouse and man (3). The only practicable method of studying long-term retention in the small species (e.g. rodents) is to increase the administered dose to a level that will render body burdens measurable for extended periods. This, however, involves the risk of injury, which might alter an animal's metabolism or, ultimately cause death.

Time patterns of retention have been followed not only for interspecies comparison but also for determination of possible relationships with certain physiological parameters within a given species. Investigators have correlated elimination characteristics with body weight, and have found linear logarithmic relationships which could best be described by functions relating retention to body weight raised to some fixed power (4, 5, 6). Numerous attempts have also been made to determine a relationship between equilibrium body burden resulting from fixed daily intake of Cs-137 and body weight.

In a study of the effect of age at the time of injection upon whole-body retention characteristics in mice, the importance of time post-injection

at various ages in metabolic schemes for intravenously administered Cs-137 is quantitated (7). The data emphasize difficulties and fallacies in fitting the retention kinetics with straightforward mathematical functions. Age has also been found to affect metabolism of Cs-137 in humans, as determined generally by whole-body counting of the assimilated fission product from fallout; however, studies of this nature are tedious because they require correction for any change in environmental fallout which may be caused by many possible natural disturbances or man-made alterations. McCraw has reviewed much of the literature on human cesium metabolism derived from such data and applied certain kinetic schemes to determine both biological half-time and radiation dose as a function of population age (8). As the many authors whom he cites have indicated, there is a definite trend toward an increased biological retention time with increased age. A list of general categories of average biological half-life for humans has been given as (9):

Infants	-	19 days
Children	-	57 days
Adult Women	-	84 days
Adult Men	-	105 days

Although the ranges about these averages are broad, they adequately serve to define a trend; however, with the changes in such variables as dietary habits with age, the many inconsistencies found in age studies are easily explained. Interestingly, adult men and women are listed separately, indicating a more rapid turnover in the latter and implying a relationship between sex and biological elimination rates. However, it has been clearly demonstrated that the total Cs-137 content per kilogram body weight at a given age is lower in women than in men, particularly after young adulthood (10). A partial explanation of these results may, therefore, be due to a sex dependent difference in body weight at a given age and a probable difference in gross body composition versus age.

Perhaps one of the most common ways of expressing Cs-137 content

(particularly in humans) is through its ratio to naturally occurring K-40. This has some rationale because of the similarity in chemical nature of the two elements and because both isotopes are easily detectable through their gamma emission. However, the ratio does depend upon certain parameters such as age, weight and lean body content and therefore should be used more as a comparative tool rather than a quantitative definition of cesium metabolism. For instance, studies on humans have shown that the cesium-to-potassium ratio changes at young adulthood (10). This is explained as the body's attempt to "discriminate" against potassium in favor of cesium. Another expression of this states that cesium retention may be quite constant but that the ratio to potassium varies because of changes in metabolism of the latter (11).

In addition to studies of normal cesium metabolism in mammals, there have been attempts to enhance excretion once the material has entered the body. Results from a recent study, using various levels of chronically fed ferric ferrocyanide following injection of Cs-137, have been encouraging, particularly when compared with those from previous investigators (12). Stress phenomena have also been used to increase the rate of cesium excretion, an example of which is alteration in environmental temperature (13).

This report deals with the whole-body retention kinetics of a group of rats that received intraperitoneal injections of large doses of Cs-137. The pattern of elimination from the body shows previously unreported characteristics which may be either a function of the many physiological parameters mentioned above or an effect of the radiation dose involved, or both. An attempt has been made to correlate these results with those from other species, particularly with the reported results of cesium behavior in man. A long component of retention is evidenced that, although not a prime contributor to the total radiation dose, comprises a major portion of the daily dose at a few months post-injection.

METHODS

Twenty male and 20 female Holtzman strain albino rats were injected

intraperitoneally with Cs-137 in isotonic saline. The dose was approximately 27 millicuries per kilogram; average body weight was 160 grams. Equal numbers of controls were maintained to serve as indicators of cross-contamination and to supply background K-40 body content.

Experimental and control rats were housed in pairs in standard cages and racks. Cages were interspersed randomly so that cage-to-cage cross-contamination could be detected. Also, since the experimental animal becomes a source of external radiation at these high internal dosages, it is preferable to randomize in the event that unexplained anomalies arise in the data. Animals were periodically whole-body counted with a collimated NaI crystal and associated electronics. Total excretion was collected routinely from individual cages and analyzed for radioactivity as a composite sample.

RESULTS

The dose of 27 millicuries per kilogram of Cs-137 delivered between two and three thousand whole-body rads to the rat over a very short (< one month) period of time and was sufficient insult to kill 50 percent of the animals in 30 days. In spite of this high early lethality rate, a few rats survived for long periods of time post-injection (see Figure 1). This small group of survivors apparently overcame the early phases of the radiation syndrome (hematological, gastrointestinal, etc.) and lived for various periods of time thereafter. This "bi-phasic" survival phenomenon has been observed previously with high-level injections of Cs-137 in experimental animals (14, 15, 16). It is the long-term retention of cesium by these few survivors that is the main concern of this report. Since the data from males and females gave essentially similar results, the two sexes are dealt with as one population.

Whole-body retention as a function of percent initial body burden versus time in days is shown in Figure 1. The smooth curve is approximated by the equation indicated and was derived by hand in the usual manner for multi-exponential functions (subtraction of successive straight line components from the curve, starting with the longest component). The ranges, although not weighted for numbers of rats, are an indication of the limited

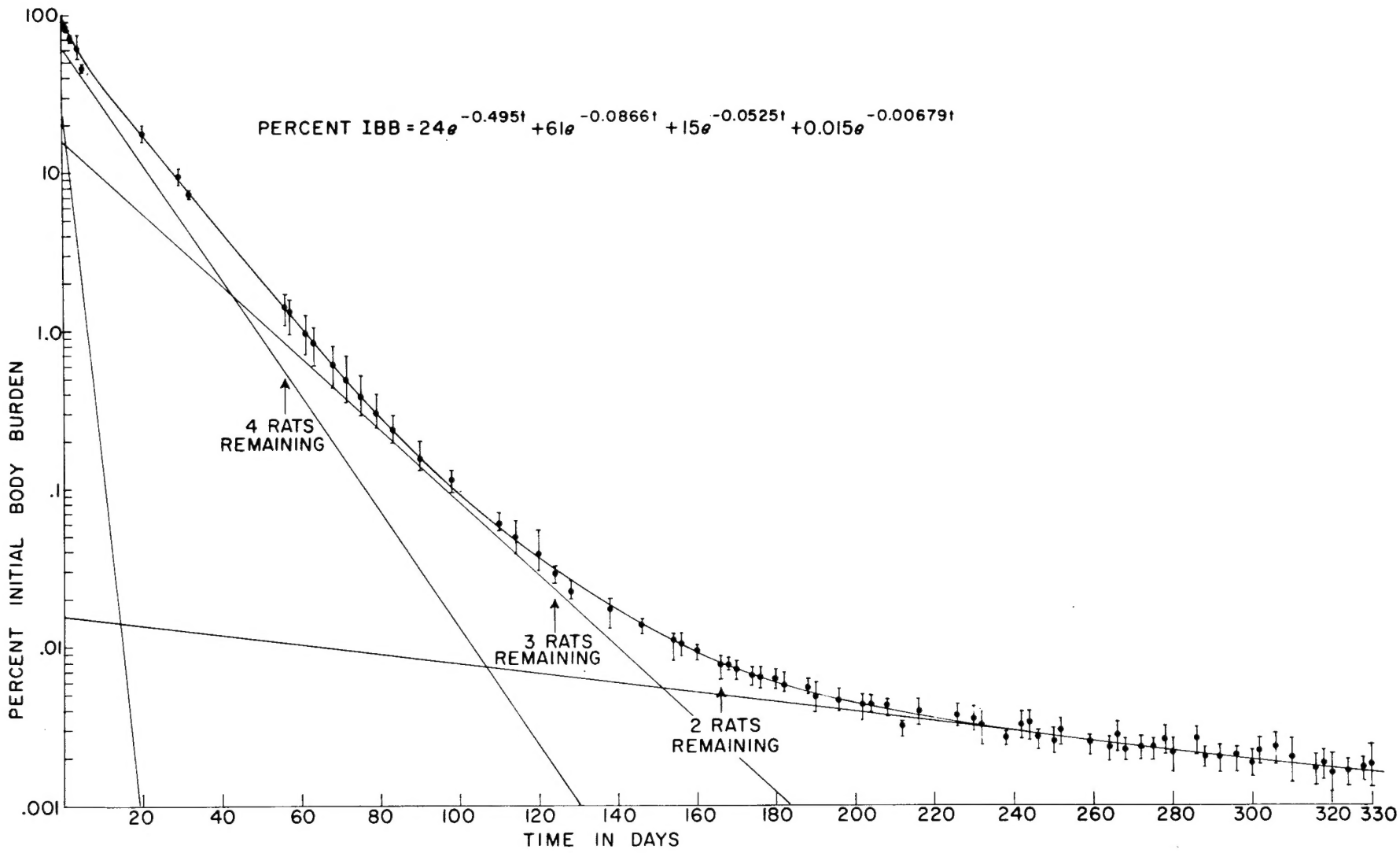

Fig. 1. Whole-body retention of Cs-137 expressed as percent of initial body burden. (The equation describes the smooth curve drawn through the mean values; the vertical line through each mean indicates the range of data points).

variability. Only two experimental animals survived beyond 170 days post-injection, one died at 335, the other at 336 days, in both cases, apparently of pneumonia. The four half-lives of whole-body elimination obtained from the percent of initial body burden versus time are: 1.4 days (24%), 8.0 days (61%), 13.2 days (15%) and 102 days (0.015%).

Extensive whole-body retention data following injection of Cs-137 in rats have been reported (3, 17). Richmond's study covered 120 days post-injection and Ballou and Thompson extended theirs to 200 days. Beyond these points, the amount of radioactivity present was apparently statistically insignificant. Figure 2, a comparison of these two sets of data with those from Figure 1, shows the similarities in kinetics. It can be speculated that, because of these similarities, all three sets of data would have been in agreement beyond 200 days had the experiments of Richmond and Ballou been terminated at a later time. To be certain that no significant contamination was present and that K-40 was not a significant contributor to the whole-body count, spectral analyses were obtained on many of the animals, including the late survivors. All γ-ray activity detected was attributable to Cs-137.

DISCUSSION

The long-term component ($T_{1/2} \cong 102$ days) is a most interesting finding. It is defined in rats for the first time and is within the range of values found from measurements on adult humans (1, 2). A discussion of these results could take many pathways; however, any detailed speculation by way of explaining the kinetics involved should await availability of more extensive data. Certain of the more general parameters which may be involved, are discussed briefly below in terms of the data presented.

Body Weight:

Increase in rat weight from time of injection to the last two deaths was approximately 1.5 (from 160 to 230 g). This factor is considerably greater than in the other two studies in Figure 2 in which rats weighed an average of 245 g at injection, a point on the growth curve where rate of increase in body weight is de-

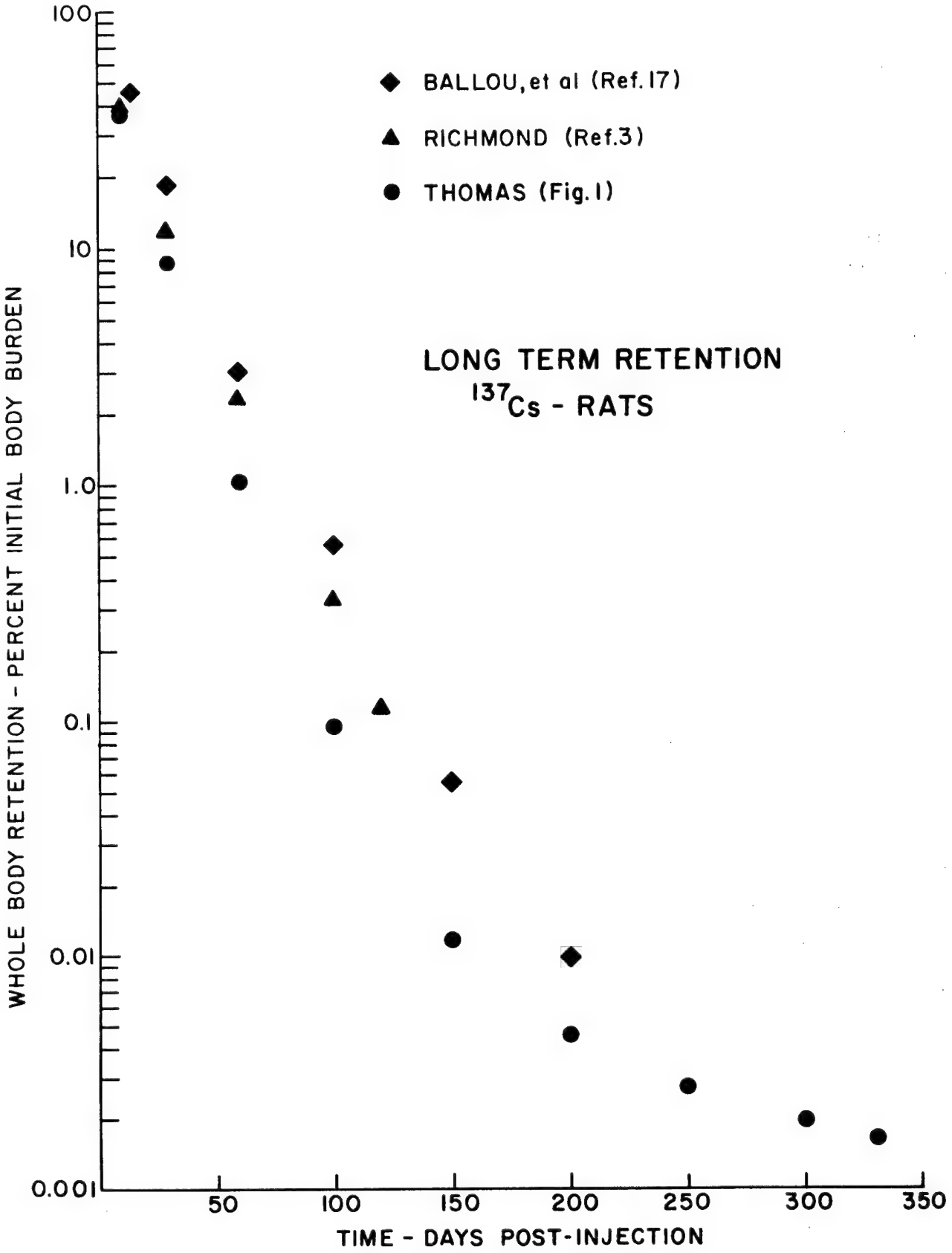

Fig. 2. A comparison of whole-body retention of Cs-137 as determined in three independent investigations.

creasing with time. It is possible, therefore, that in the younger animals where shorter half-lives exist, growing organs and generally higher state of physical activity may make available more deposited cesium for turnover. However, as the rate of increase in body and organ weight decreases with time, a more passive state may exist. This would help to explain the longer half-times observed in the heavier animals.

Age:

It is difficult to separate age and weight of an animal because they generally relate to each other. However, at least one interesting analogy between rat and man can be found using age alone as a criterion. In young adulthood, the amount of cesium in the body appears to stabilize and the half-life of retention exceeds 100 days (10). If young adulthood in humans is 20-25 years and average life-span is 65-75 years, then this change in cesium metabolism occurs when approximately one-third of normal life has been expended. In rats, this would occur at approximately 200 days of life or 120-160 days post-injection based upon the average control life span of 550-600 days. It is possible then, that this age factor applies to rats as well as man, that it has not been detected previously because of analytical limitations, and that it may be present in other species.

Radiation Effect:

Radiation energy absorbed from Cs-137 β-particles summates to a large whole-body dose (2-3000 rads) in a short time, at the injected dose level used. The γ-ray dose which these animals received, either from the deposited Cs-137 or from the other animals, acting as external sources, although not negligible, is low compared to the β-particle contribution. In some cases, it could amount to as high as five percent of the total dose but most often it is a very much smaller contributor. It has not been determined precisely what effects this total radiation insult may have on specific facets of cesium metabolism. However, as a

part of the generalized radiation syndrome which rapidly ensues, there no doubt is an effect upon mineral metabolism and ion balance. With the emaciation which accompanies these high levels, the muscle, one of the primary sites of cesium deposition, would be expected to have a disturbed metabolism and an alteration in potassium behavior.

One major argument against a dramatic radiation effect upon Cs-137 retention in this study is the similarity to the other studies in Figure 2. Sizable early changes could have been anticipated but are not evident. However, with no lower level data for comparison, it could be assumed that the long half-life component is radiation induced and may be a late radiation effect. Similar experiments at lower injection levels are underway to determine if a dose gradient is reflected by alteration in the retention pattern.

Other Pertinent Factors:

Rate of change of the ratio of cesium to potassium diminishes at young adulthood in humans (10). The ratio more or less stabilizes and individual half-lives of retention appear steady (within limits) throughout adult life, indicating a qualitatively similar metabolic scheme. In the present studies, no Cs-137 to K-40 ratios were obtained on the same animal; however, since the age-retention relationship is consistent with findings on humans, the ratio probably follows a similar pattern.

The sex-related retention difference found by some investigators could not be verified in this study perhaps because of the limited number of animals; however, whatever the underlying reason for the relation between sex and retention, its existence in other species implies that it also holds for rodents. If weight is a significant factor in the sex differences observed, then the fact that female rats seldom reach the size of males might be pertinent. Again, for a given age, the reported sex difference may be a function of body weight, in which case it is not necessarily a true sex (hormonal) related discrepancy.

Diet is an important factor in Cs-137 retention and uptake in humans due to individual eating habits as well as to variations in environmental content from fallout. For example, in humans periodically observed for about nine years, it was found that the smaller variations in cesium body content were due to dietary habits rather than to alterations in general fallout levels (18). However, in the experimental studies reported here, the body levels of Cs-137 were so much higher than could be derived from daily food intake that any contribution therefrom would be negligible. This is verified by spectral analyses on control rats which also indicated a negligible amount of radioactivity.

SUMMARY

A long-term component of Cs-137 whole-body retention in rats has been presented. Analogies have been made between these and similar data obtained from animal studies and measurements on humans. Certain broad physiological parameters such as age, body weight, and sex have been discussed relative to observed retention kinetics. Similarity in half-lives of body loss have been compared for man and rodent based upon the limited pertinent experimental data available.

The radiation level in this study was high and its effect upon cesium behavior is not clear. However, experiments at a lower dose are underway to help quantitate the effect of continued insult from the deposited radioactive material.

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